ACKNOWLEDGMENTS

We thank Dr. Takeharu Yamanaka Dr. Shinichiro Nakamura, Mr. Kouichi Hosoda, and other staff members of WJTOG datacenter for data management.

Table1. patient Characteristics

Characteristic	Arm A (%)	Arm B (%)	Arm C (%)	P value
Sex				P=0.879
Female	18(12.3%)	21(14.3%)	19(12.9%)	
Male	126(87.7%)	126(85.7%)	128(87.1%)	
Age				P=0.378
Median(range)	63.0(31-74)	62.0(30-74)	63.0(38-74)	
>=70	27(18.5%)	36(24.5%)	31(21.1%)	
Smoking history				P=0.240
Absence	17(11.6%)	15(10.2%)	9(6.1%)	
Presence	129(88.4%)	132(89.8%)	138(93.9%)	
Performance status				P=0.447
0	56(38.4%)	66(44.9%)	65(44.2%)	
1	90(61.6%)	81(55.1%)	81(55.1%)	
Unknown	0(0.0%)	0(0.0%)	1(0.7%)	
Weight loss during the previous 6month period				P=0.680
<5%	92(63.0%)	100(68.0%)	95(64.6%)	
≥5%	28(19.2%)	24(16.3%)	29(19.7%)	
Unknown	26(17.8%)	23(15.6%)	23(15.6%)	
Staging				P=0.901
IIIA	49(33.6%)	46(31.3%)	49(33.3%)	
IIIB	97(66.4%)	101(68.7%)	98(66.7%)	
N status				-
N2	94(64.4%)	86(58.5%)	99(67.3%)	
N3	33(22.6%)	43(29.3%)	32(21.8%)	
Histology				-
Adenocarcinoma	58(39.7%)	69(46.9%)	62(42.2%)	
Squamous cell carcinoma	70(47.9%)	62(42.2%)	71(48.3%)	

Table 2. Chemotherapy Administered

	No.of Patients (%)			
	Arm A	Arm B	Arm C	
No,of cycles				
Concurrent chemotherapy Cycles				
1	18.5	0.7	2.0	
2	81.5	2.0	2.0	
3		5.4	1.4	
4		24.5	6.8	
5		26.5	29.3	B vs C : P=0.003
6		40.8	58.5	B vs C : P<0.001
Consolidation Chemotherapy				
0	46.6	34.0	30.6	
1	12.3	36.7	19.7	
2	41.1	29.3	49.7	A vs B vs C : P=0.002

Table 3. Toxicity (>=Grade3)

	All Treatment				Concurrent Phase			
	Arm A	Arm B	Arm C	P value	Arm A	Arm B	Arm C	P value
Neutropenia	95.9%	60.5%	61.9%	<0.001	93.8%	53.7%	23.1%	<0.001
Leukopenia	96.6%	75.5%	66.0%	<0.001	95.9%	72.1%	46.9%	<0.001
Anemia	25.3%	17.7%	8.8%	<0.001	15.8%	8.8%	6.1%	0.019
Thrombocyto penia	28.8%	28.6%	7.5%	<0.001	21.9%	11.6%	5.4%	<0.001
Febrile neutropenia	37.0%	8.8%	10.2%	<0.001	30.8%	6.1%	3.4%	<0.001
Nausea	21.9%	4.8%	4.8%	<0.001	21.9%	3.4%	3.4%	<0.001
Vomiting	6.8%	2.7%	0.7%	0.012	6.2%	1.4%	0.0%	0.001
Fatigue	13.0%	6.1%	4.8%	0.019	9.6%	2.0%	1.4%	<0.001
Constipation	11.6%	6.1%	2.7%	0.009	8.9%	6.1%	1.4%	0.015
Diarrhea	0.7%	2.0%	1.4%	0.606	0.7%	0.7%	0.7%	0.999
Neurogenic(sensory)	0.7%	0.7%	4.8%	0.017	0.0%	0.0%	0.0%	–
Esophagitis	5.5%	2.7%	8.2%	0.121	4.1%	2.0%	7.5%	0.077
Infection	26.0%	16.3%	17.0%	0.066	22.6%	12.2%	10.2%	0.006
Dyspnea	6.2%	5.4%	6.1%	0.957	2.7%	0.7%	2.0%	0.406
Pneumonitis	1.4%	4.1%	4.1%	0.312	0.0%	0.0%	0.7%	0.368

Table 4. Objective response

Treatment group		Group A	Group B	Group C
Number of the patients		146	147	147
Response	CR	3 (2.1%)	4 (2.7%)	5 (3.4%)
	PR	94 (64.4%)	79 (53.7%)	88 (59.9%)
	SD	16 (11.0%)	32 (21.8%)	32 (21.8%)
	PD	19 (13.0%)	19 (12.9%)	16 (10.9%)
	NE	14 (9.6%)	13 (8.8%)	6 (4.1%)
Response Rate	CR+PR	97 (66.4%)	83 (56.5%)	92 (63.0%)
		P=0.198		

Figure 1.

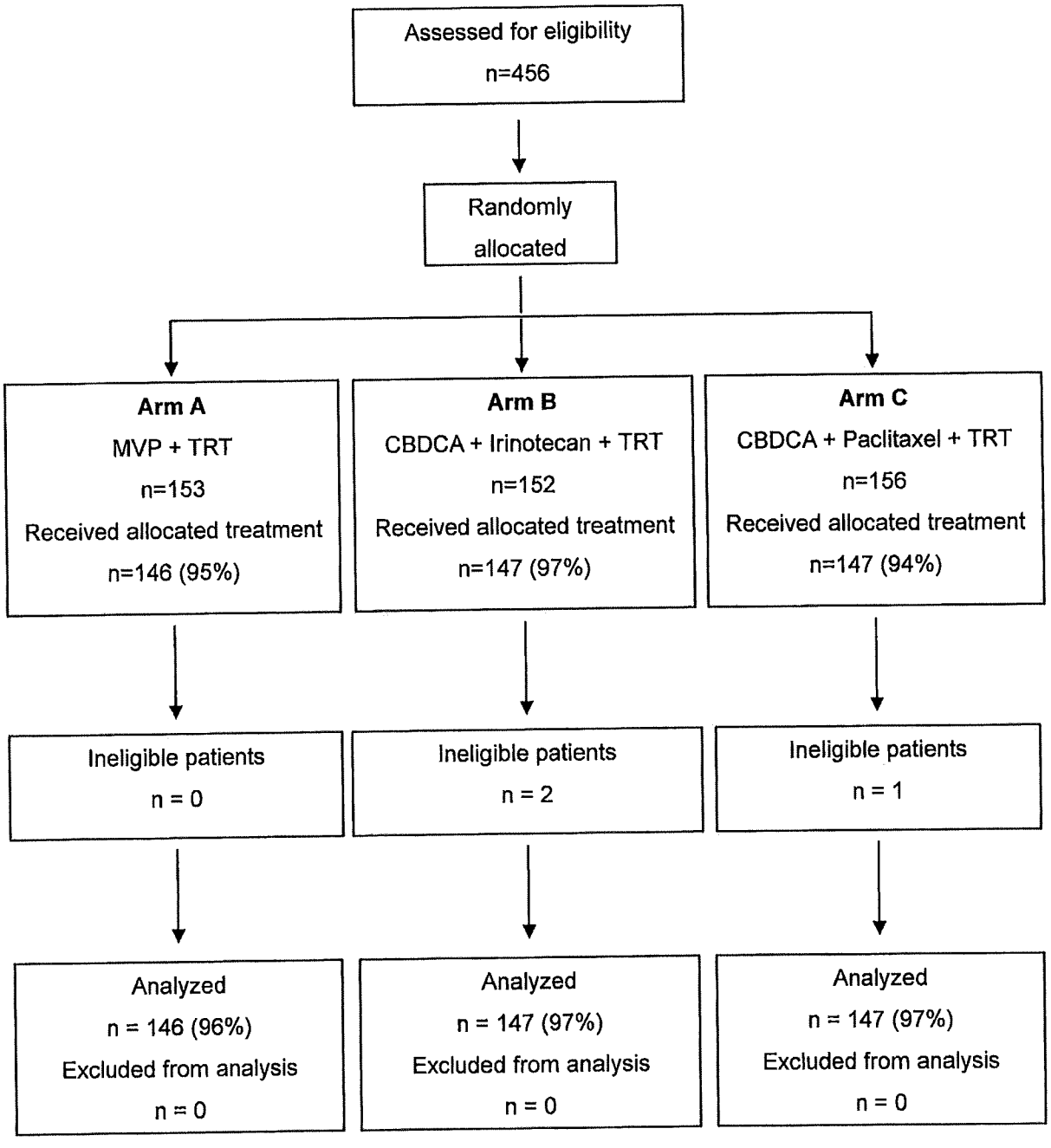

Assessed for eligibility
n=456
Randomly allocated
Arm A
MVP + TRT
n=153
Received allocated treatment
n=146 (95%)
Arm B
CBDCA + Irinotecan + TRT
n=152
Received allocated treatment
n=147 (97%)
Arm C
CBDCA + Paclitaxel + TRT
n=156
Received allocated treatment
n=147 (94%)
Ineligible patients
n = 0
Ineligible patients
n = 2
Ineligible patients
n = 1
Analyzed
n = 146 (96%)
Excluded from analysis
n = 0
Analyzed
n = 147 (97%)
Excluded from analysis
n = 0
Analyzed
n = 147 (97%)
Excluded from analysis
n = 0

Figure 2. Schema of Treatment schedule

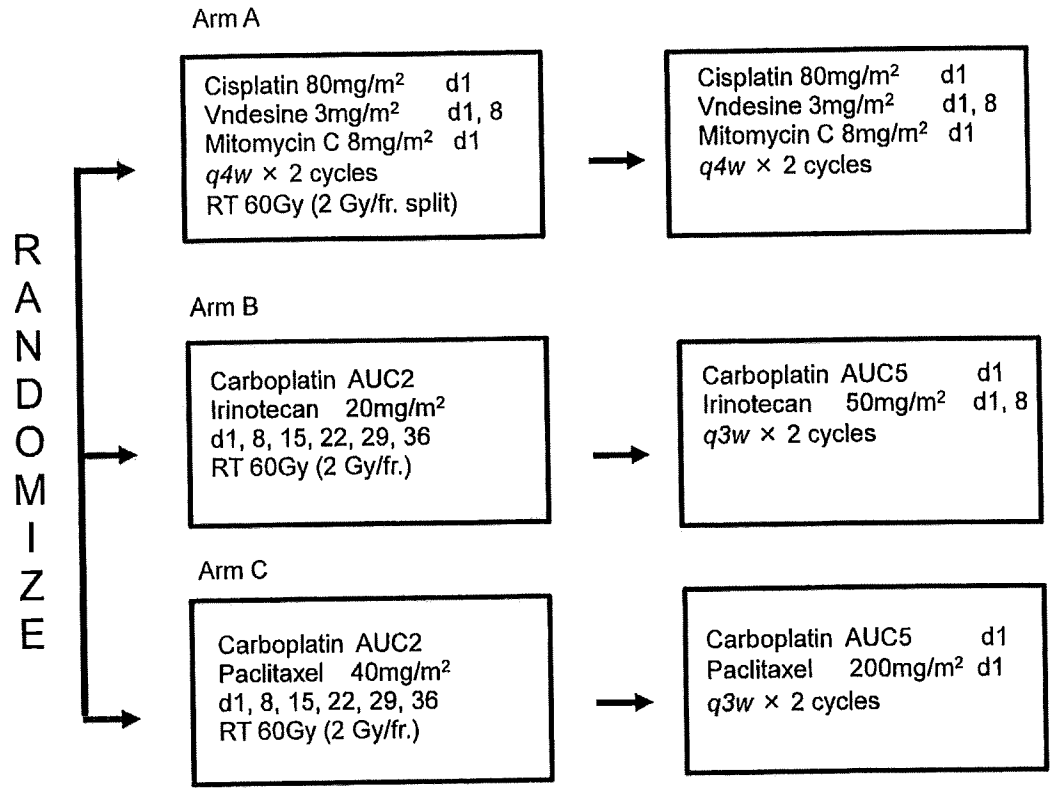
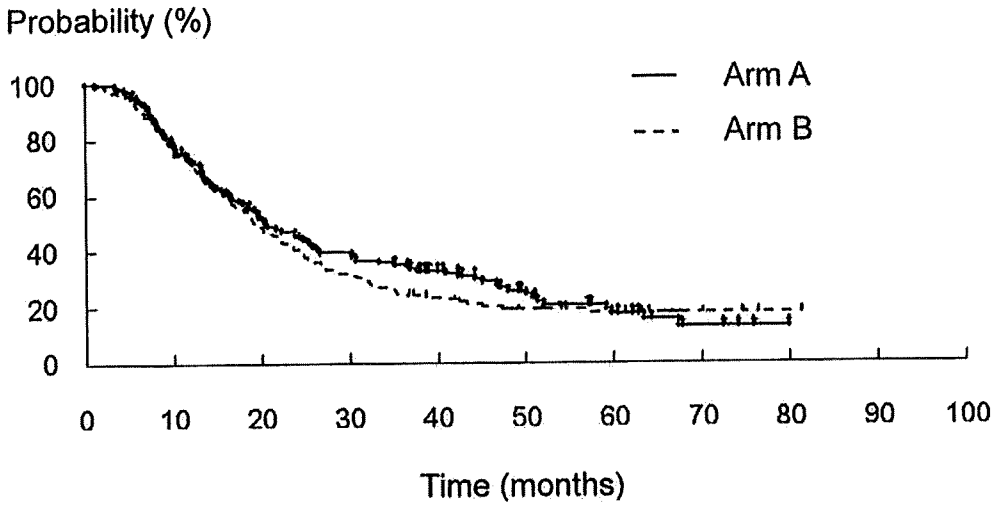


Figure 3a.


Probability (%)
100
80
60
40
20
0
Arm A
Arm B
0
10
20
30
40
50
60
70
80
90
100
Time (months)

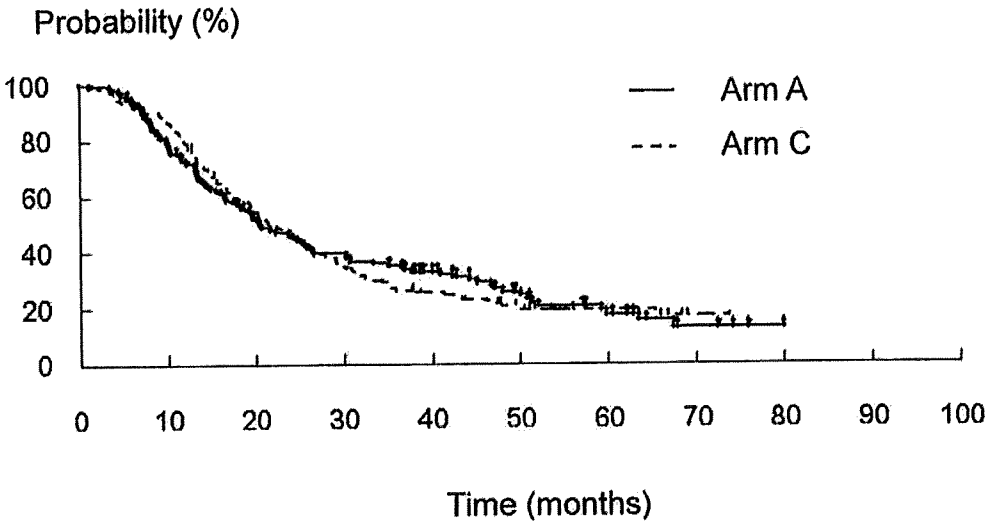
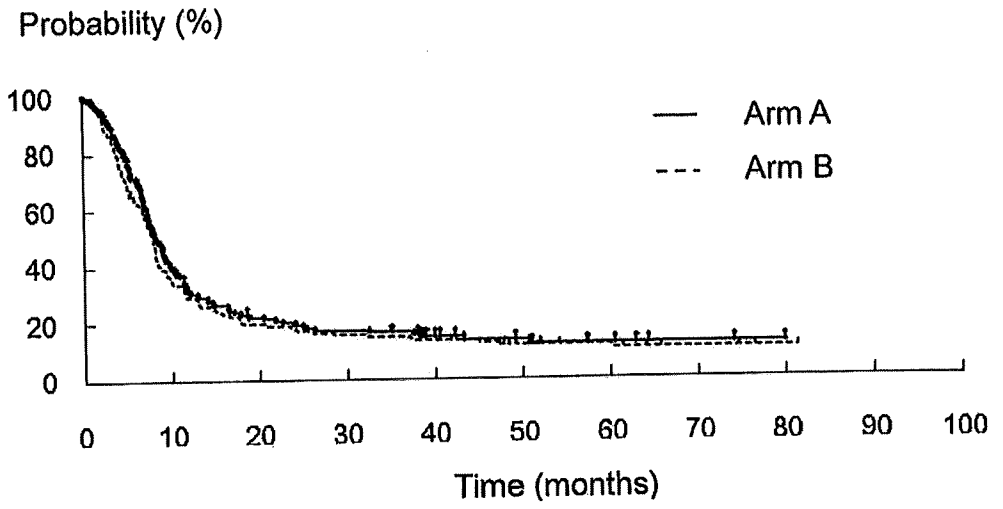
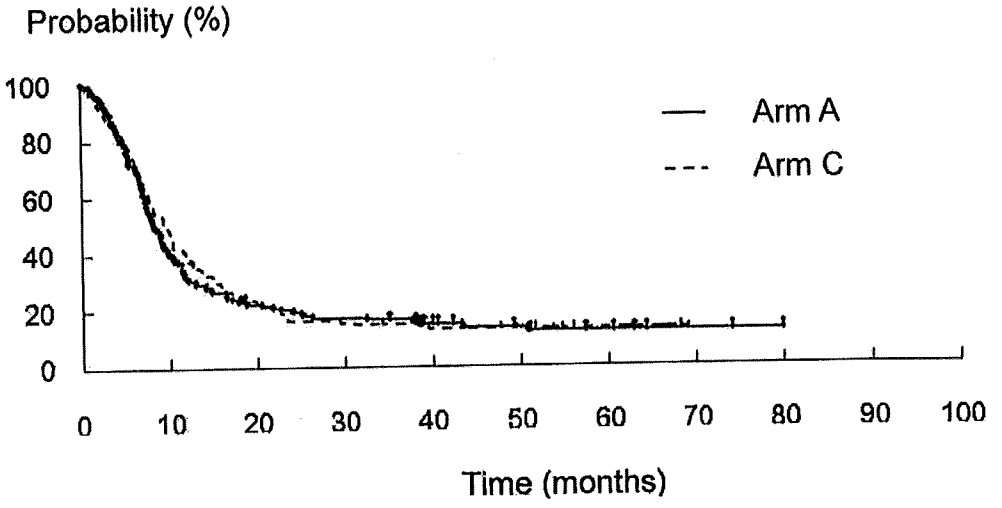

Probability (%)
100
80
60
40
20
0
Arm A
Arm C
0
10
20
30
40
50
60
70
80
90
100
Time (months)

Figure 3b.


Probability (%)
100
80
60
40
20
0
Arm A
Arm B
0
10
20
30
40
50
60
70
80
90
100
Time (months)


Probability (%)
100
80
60
40
20
0
Arm A
Arm C
0
10
20
30
40
50
60
70
80
90
100
Time (months)

Combined Survival Analysis of Prospective Clinical Trials of Gefitinib for Non-Small Cell Lung Cancer with *EGFR* Mutations

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Abstract

Purpose: Somatic mutations of the epidermal growth factor receptor (*EGFR*) gene are associated with an increased response to gefitinib in patients with non-small cell lung cancer. We have examined the impact of gefitinib on progression-free survival and overall survival in patients with *EGFR* mutation-positive non-small cell lung cancer.

Experimental Design: We searched for all clinical trials that prospectively evaluated the efficacy of gefitinib for advanced non-small cell lung cancer with *EGFR* mutations in Japan. We did a combined analysis based on individual patient data from the identified trials.

Results: Seven eligible trials were identified for a total of 148 non-small cell lung cancer patients with *EGFR* mutations. The overall response rate to gefitinib was 76.4% [95% confidence interval (95% CI), 69.5-83.2]. The median progression-free survival and overall survival were 9.7 months (95% CI, 8.2-11.1) and 24.3 months (95% CI, 19.8-28.2), respectively. Good performance status and chemotherapy-naïve status were significantly associated with a longer progression-free survival or overall survival. Of the 148 patients, 87 received gefitinib as a first-line therapy, whereas 61 received systemic chemotherapy before gefitinib treatment. The median progression-free survival after the start of first-line therapy was significantly longer in the gefitinib-first group than in the chemotherapy-first group (10.7 versus 6.0 months; $P < 0.001$), whereas no significant difference in median overall survival was apparent between the two groups (27.7 versus 25.7 months; $P = 0.782$).

Conclusions: Gefitinib monotherapy confers substantial clinical benefit in terms of progression-free survival and overall survival in non-small cell lung cancer patients with *EGFR* mutations. Randomized trials comparing chemotherapy with gefitinib as a first-line treatment are warranted in such patients.

Non-small cell lung cancer is the leading cause of death related to cancer worldwide (1). Cytotoxic chemotherapy remains the mainstay of treatment for patients with metastatic non-small cell lung cancer on the basis of the associated moderate improvement in survival and quality of life (2-4). The poor outlook even for patients with advanced non-small cell lung cancer who receive such chemotherapy has prompted a search for new therapeutic approaches.

The epidermal growth factor receptor (EGFR) is frequently overexpressed in non-small cell lung cancer and has been implicated in the pathogenesis of this disease (5, 6). Given the biological importance of EGFR signaling in non-small cell lung cancer, EGFR-specific tyrosine kinase inhibitors, including gefitinib and erlotinib, have been extensively studied in patients with this condition (7-10). We and others have shown that a clinical response to these agents is more common in women than in men, in Japanese than in individuals from Europe or the United States, in patients with adenocarcinoma than in those with other histologic subtypes of cancer, and in individuals who have never

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Translational Relevance

Somatic mutations of the epidermal growth factor receptor (EGFR) are associated with response of advanced non–small cell lung cancer to EGFR-specific tyrosine kinase inhibitors such as gefitinib and erlotinib. Prospective phase II trials of gefitinib monotherapy for advanced non–small cell lung cancer with *EGFR* mutations have found higher response rates than those observed with conventional chemotherapy. However, overall survival data have not been available because of the short follow-up period in these trials. We have now analyzed updated individual patient data from seven Japanese prospective phase II trials of gefitinib monotherapy, including a total of 148 *EGFR* mutation–positive individuals. We found that gefitinib confers a highly favorable progression-free survival (9.7 months) and overall survival (24.3 months) in such patients. Furthermore, an exploratory comparison between gefitinib and systemic chemotherapy in the first-line setting suggests that gefitinib monotherapy is an effective first-line treatment for *EGFR* mutation–positive non–small cell lung cancer. These results have potentially important implications for the treatment of non–small cell lung cancer associated with *EGFR* mutations.

smoked than in those with a history of smoking (11). Somatic activating mutations in the EGFR gene (*EGFR*) have also been identified as a major determinant of the clinical response to treatment with gefitinib or erlotinib (12–14). *EGFR* mutations are present more frequently in never-smokers, females, individuals with adenocarcinoma, and patients of East Asian ethnicity (15–18), the same groups identified clinically as most likely to respond to treatment with EGFR tyrosine kinase inhibitors.

Several prospective clinical trials of gefitinib or erlotinib for treatment of non–small cell lung cancer patients with *EGFR* mutations have been done to date (18–26). These trials have shown radiographic response rates ranging from 55% to 82% and a median progression-free survival of 8.9 to 13.3 months. These values are three to four times those historically observed with platinum-based chemotherapy as a first-line treatment for advanced non–small cell lung cancer. As the data accumulate, it seems clear that non–small cell lung cancer patients with *EGFR* mutations exhibit a distinct clinical response to treatment with EGFR tyrosine kinase inhibitors. An improvement in overall survival conferred by treatment with these drugs is also expected in patients harboring *EGFR* mutations. However, it was not possible to evaluate overall survival in most of the clinical trials at the time of publication because the number of patients was not sufficiently large and the follow-up period was not long enough to obtain precise estimates of survival outcome.

We have now done a combined analysis based on individual patient data from prospective phase II trials of gefitinib monotherapy in non–small cell lung cancer patients with *EGFR* mutations. The present study was designated I-CAMP for Iressa Combined Analysis of Mutation Positives. Our main aim was to update the effects of gefitinib treatment on survival end points in the selected population of patients. We further explored the efficacy of gefitinib administration as a first-line treatment for *EGFR* mutation–positive patients in comparison with conventional cytotoxic chemotherapy.

Materials and Methods

Study selection. We searched for all clinical trials conducted in Japan that prospectively evaluated the efficacy of gefitinib monotherapy for advanced non–small cell lung cancer associated with *EGFR* mutations. The search was done with PubMed and the Proceedings of the American Society of Clinical Oncology covering the period from 2004 to 2008. Seven phase II trials were identified, all of which were published (19–25). All identified trials, including genomic analysis of stored or collected tumor tissue, were approved by institutional review boards, and *EGFR* mutations were determined either by direct sequencing, by common fragment analysis of PCR-mediated amplification products for exon 19 deletions and cycleave real-time PCR for the L858R point mutation (26), or by the peptide nucleic acid–locked nucleic acid PCR clamp method (27). All trials had the same treatment schedule, consisting of the oral administration of 250 mg of gefitinib once a day. In some trials, gefitinib was the first-line treatment, whereas in others, it was administered after cytotoxic chemotherapy. The primary end point of these trials was tumor response rate, which was assessed according to the Response Evaluation Criteria in Solid Tumors (28).

Collection of individual patient data. The study was done in accordance with the Declaration of Helsinki (1964, amended in 2000) and the Ethical Guidelines for Epidemiologic Study (Ministry of Health, Labor, and Welfare of Japan, 2002). The primary objective of the study was to determine the impact of gefitinib treatment for *EGFR* mutation–positive non–small cell lung cancer on overall survival on the basis of examination of individual data from 148 patients enrolled in the seven selected trials. Secondary objectives included evaluation of response, progression-free survival, and safety for gefitinib, and to compare progression-free survival and overall survival for first-line gefitinib treatment with those for first-line chemotherapy administered before gefitinib. The medical records of patients in the seven identified studies were reviewed for patient characteristics, drug side effects, tumor response, progression-free survival, and overall survival. Patient characteristics noted included sex, age, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, tumor-node-metastasis staging, postoperative disease recurrence, smoking history, previous chemotherapy, and type of *EGFR* mutation. All adverse events with a grade of ≥3 according

Table 1. Patient characteristics

Characteristic	No. of patients (n = 148)
Histology (adeno/nonadeno)	143/5
Median age (range), y	65 (33-89)
Sex (female/male)	102/46
Smoking status (never-smoker/smoker)	105/43
Tumor stage (IIIB/IV)	19/129
ECOG PS (0/1/2/3/4)	58/69/14/3/4
No. of previous chemotherapy regimens (0/1/2/3)	85/48/14/1
EGFR mutation (ex 19 del/L858R/other*)	88/56/4

Abbreviations: adeno, adenocarcinoma; nonadeno, nonadenocarcinoma; PS, performance status; ex 19 del, exon 19 deletion.
*Exon 19 deletion + L747P, L858R + L858K, exon 19 deletion + 26-bp deletion + AT insertion, or exon 19 deletion + L858R.

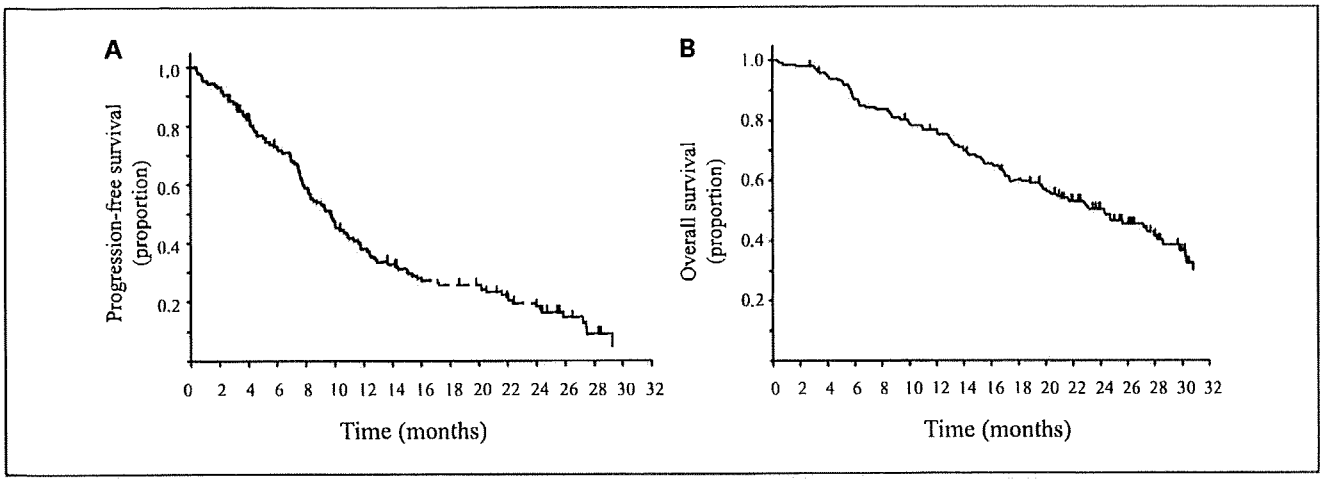

Fig. 1. Kaplan-Meier analysis of progression-free survival (*A*) and overall survival (*B*) for all 148 patients after initiation of gefitinib treatment.

to the National Cancer Institute-Common Toxicity Criteria (version 3.0) were recorded, as was interstitial lung disease of any grade. The clinical data for first-line chemotherapy administered before gefitinib were obtained retrospectively. In accordance with Response Evaluation Criteria in Solid Tumors, objective tumor responses were classified as complete response, partial response, stable disease, or progressive disease. For analysis of progression-free survival and overall survival, the day of initiation of gefitinib treatment, the day tumor progression was detected, and the last day that survival was evaluated or the day of death were noted. In addition, clinically important prognostic factors were examined.

Statistical analysis. Overall survival was defined as the time from the initiation of gefitinib monotherapy until death from any cause. Progression-free survival was defined as the time from the initiation of gefitinib monotherapy to the first observation of disease progression or death from any cause. Progression-free survival and overall survival were analyzed by the Kaplan-Meier method and were compared between groups by the log-rank test. Prognostic factors for progression-free survival and overall survival were examined by the Cox regression model, with adjustment for covariates, including sex (female versus male), smoking history (never-smoker versus smoker), tumor-node-metastasis stage (IIIB versus advanced), ECOG performance status (0 or 1 versus 2 to 4), the number of previous chemotherapy regimens (0 versus 1 to 3), and type of *EGFR* mutation (L858R versus exon 19 deletion). Differences in characteristics between patient groups according to first-line therapy were evaluated by the χ^2 test. A P of <0.05 was considered statistically significant.

Results

Patient characteristics. The characteristics of the 148 *EGFR* mutation-positive non-small cell lung cancer patients are summarized in Table 1. The median age was 65 years, with a range of 33 to 89 years. A total of 102 patients (69%) were women, and 105 patients (71%) were never-smokers. The most common tumor histology was adenocarcinoma, which was present in 143 patients (97%). Whereas 88 patients had a single *EGFR* mutation consisting of an exon 19 deletion, 56 patients had a single mutation consisting of L858R in exon 21 and the remaining 4 patients had double or triple mutations involving an exon 19 deletion or L858R.

Drug safety and toxicity. Most treatment-related toxicity was mild, being of National Cancer Institute-Common Toxicity Criteria grade 1 or 2. Adverse events of grade 3 or 4 included skin rash (2.7%), diarrhea (1.4%), interstitial lung disease (2.7%), and abnormal liver function, including elevated aspartate aminotransferase or alanine aminotransferase (8.1%). There were no treatment-related deaths.

Response and survival. Eleven patients (7%) showed a complete response and 102 individuals (69%) achieved a partial response to gefitinib monotherapy, yielding an objective response rate of 76.4% [95% confidence interval (95% CI), 69.5-83.2] and substantiating the individual observations of

Table 2. Cox regression analysis of progression-free survival and overall survival after gefitinib treatment (n = 148)

Variable	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex (female/male)	0.63	0.37-1.09	0.098	0.65	0.35-1.22	0.182
Never-smoker/smoker	0.93	0.51-1.66	0.794	0.82	0.42-1.61	0.570
Tumor stage (IIIB/IV)	1.42	0.81-2.48	0.219	1.83	0.96-3.48	0.067
ECOG PS (0-1/2-4)	0.58	0.33-1.01	0.056	0.27	0.15-0.48	<0.0001
Previous chemotherapies (0/1-3)	0.57	0.38-0.86	0.007	0.60	0.37-0.95	0.031
EGFR mutation (L858R/ex 19 del)	0.93	0.62-1.40	0.730	0.83	0.52-1.33	0.438

Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Table 3. Patient characteristics at the onset of first-line treatment with gefitinib or chemotherapy

Characteristic	Gefinitib (n = 87)	Chemotherapy (n = 61)	P
Histology (adeno/nonadeno)	85/2	58/3	0.403
Median age (range), y	66 (33-89)	61 (33-79)	0.032
Sex (female/male)	64/23	38/23	0.145
Smoking status (never-smoker/smoker)	68/19	37/24	0.021
Tumor stage (IIIB/IV)	8/79	11/50	0.111
ECOG PS (0/1/2/3/4)	33/37/11/3/3	25/32/3/0/1	0.026
EGFR mutation (ex 19 del/L858R/other)	50/36/1	38/20/3	0.256

NOTE: *P*s for differences between the two groups of patients were determined by the χ^2 test, with that for ECOG performance status being determined for comparison of the proportion of patients with a status of 2 to 4.

each of the relatively small phase II trials. Twenty-three patients (16%) had stable disease, and nine (6%) had progressive disease.

At the time of analysis, the median follow-up time was 20.7 months. The median progression-free survival was 9.7 months (95% CI, 8.2-11.1), and the 1-year progression-free survival rate was 37.7% (95% CI, 29.7-45.7; Fig. 1A). The median overall survival was 24.3 months (95% CI, 19.8-28.2), and the 1-year overall survival rate was 76.7% (95% CI, 69.8-83.6; Fig. 1B). Cox regression analysis revealed that an ECOG performance status of 0 or 1 and chemotherapy-naïve status were significantly associated with a longer progression-free survival or overall survival (Table 2).

Comparison between gefitinib and cytotoxic chemotherapy as first-line treatment. Of the 148 *EGFR* mutation-positive non-small cell lung cancer patients, 87 received gefitinib as first-line therapy whereas 61 received systemic chemotherapy as first-line treatment, followed by gefitinib. Clinical information was assembled retrospectively for the patients who received first-line chemotherapy before gefitinib treatment. The clinicopathologic data for these two groups of patients are shown in Table 3. The proportion of patients with a poor ECOG performance status ($\geq$2) was higher in the first-line gefitinib group (20%) than in the first-line chemotherapy group (7%; P = 0.026). The response rate was significantly higher for the first-line gefitinib group than for the first-line chemotherapy group (79.3% versus 24.6%; $P < 0.001$; Table 4). Kaplan-Meier analysis of progression-free survival and overall survival after the start of first-line antitumor therapy is shown in Fig. 2. The log-rank test revealed that progression-free survival was significantly longer in the first-line gefitinib group than in the first-line chemotherapy group (median of 10.7 versus 6.0 months; Fig. 2A), whereas there was no significant difference in overall survival between the two groups of patients (median of 27.7 versus 25.7 months, respectively; Fig. 2B). Cox regression analysis yielded similar results for progression-free survival and overall survival.

Discussion

EGFR mutations were first associated with non-small cell lung cancer in 2004, and several prospective phase II trials of gefitinib or erlotinib for treatment of non-small cell lung cancer patients with activating *EGFR* mutations have subsequently been reported (12-14). The primary end point of these prospective trials was objective response rate, with the result that overall survival data were not complete because of the short follow-up periods. We have now analyzed the updated individual data for 148 *EGFR* mutation-positive non-small cell lung cancer patients enrolled in seven prospective phase II trials of gefitinib monotherapy in Japan. The median progression-free survival and overall survival were 9.7 months (95% CI, 8.2-11.1) and 24.3 months (95% CI, 19.8-28.2), respectively. These findings reveal a markedly improved outcome with gefitinib therapy compared with that typically observed with systemic chemotherapy in patients with advanced non-small cell lung cancer.

The number of *EGFR* mutation-positive patients examined in the present study is sufficient to allow comparison of progression-free survival and overall survival among non-small cell lung cancer patients with different clinicopathologic characteristics. Previous studies have shown that *EGFR* mutations are more frequent in females, individuals with no history of smoking, and patients with adenocarcinoma, and that these characteristics are also associated with a higher response rate and longer survival after gefitinib treatment (16-18). We have now found that sex and smoking status were not significantly associated with progression-free survival or overall survival among patients with *EGFR* mutations, indicating that such mutations, regardless of sex and smoking status, are the most appropriate determinant for gefitinib treatment. These findings suggest that analysis of *EGFR* mutation status is warranted for

Table 4. Tumor response to first-line treatment with gefitinib or chemotherapy

Tumor response	Gefitinib	Chemotherapy*
Complete response	7	0
Partial response	62	15
Stable disease	11	31
Progressive disease	6	10
Unknown	1	5
Total	87	61
Response rate (95% CI), %	79.3 (70.8-87.8)	24.6 (13.8-35.4)

NOTE: $P < 0.001$ for difference in response rate between the two groups (χ^2 test).
*The chemotherapy regimens included platinum doublet (n = 39), nonplatinum doublet (n = 8), single agent (n = 9), and unknown (n = 5).

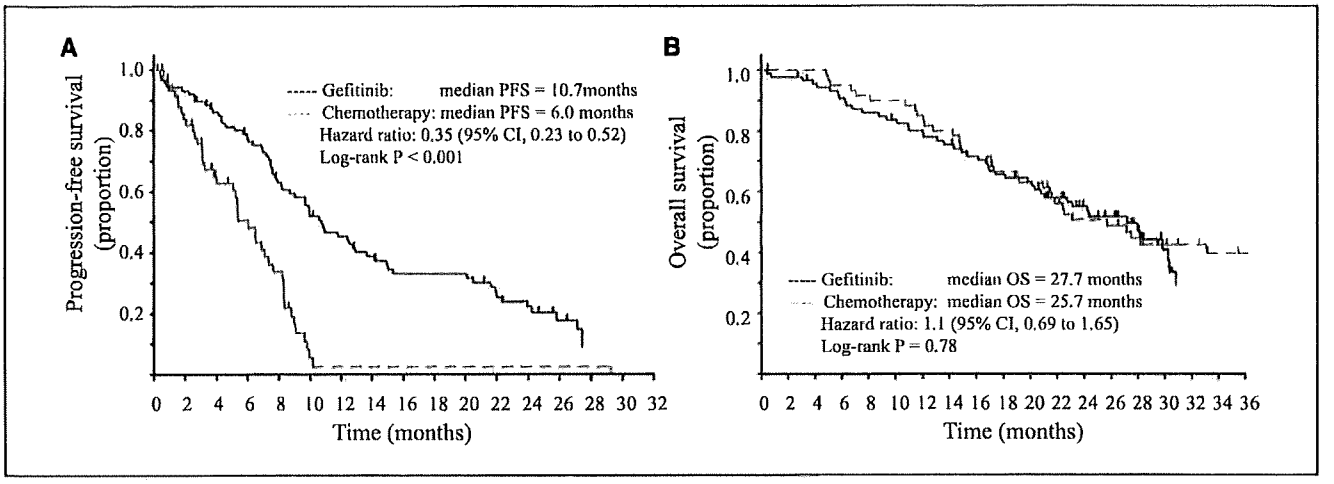

Fig. 2. Comparison of progression-free survival (*A*) or overall survival (*B*) after the initiation of first-line treatment with gefitinib or chemotherapy.

treatment selection even in male smokers with adenocarcinoma. Studies on North American patients have indicated that those with deletions of exon 19 of *EGFR* have a better response rate, progression-free survival, and overall survival after EGFR tyrosine kinase inhibitor treatment than do those with the L858R mutation in exon 21 (33, 34); however, the present study did not detect a significant difference in progression-free survival or overall survival between the gefitinib-treated patients with exon 19 deletions and those with L858R. Our finding is consistent with previous retrospective analysis of East Asian cohorts showing similar survival benefit of EGFR tyrosine kinase inhibitor treatment in patients with either type of mutation (35, 36). This apparent difference between North American and East Asian populations might be due to the type of EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) studied, given that all patients in the East Asian cohorts and our present study were treated with gefitinib whereas the North American patients included those treated with erlotinib or gefitinib. Although the biological basis for a possible ethnic difference in EGFR tyrosine kinase inhibitor efficacy according to the type of *EGFR* mutation remains unknown, it seems that East Asian patients with exon 19 deletions or with L858R benefit equally from gefitinib treatment.

Platinum-based doublet chemotherapy is the standard of care for most patients with advanced non-small cell lung cancer (2, 3). The substantial clinical benefits of gefitinib treatment in *EGFR* mutation-positive non-small cell lung cancer patients raise the question about whether first-line gefitinib treatment is more beneficial than systemic chemotherapy in this genotype-defined population. Given that the impact of first-line systemic chemotherapy on *EGFR* mutation-positive non-small cell lung cancer patients has not been fully evaluated, we compared progression-free survival and overall survival between mutation-positive patients who received first-line gefitinib treatment and those treated initially with systemic chemotherapy. We found that first-line gefitinib treatment yielded a significantly longer progression-free survival than did systemic chemotherapy in *EGFR* mutation-positive non-small cell lung cancer patients, supporting the use of gefitinib as an initial therapy in this patient population. This finding is consistent with a subset analysis of a recently completed randomized phase III study known as Iressa Pan-Asia Study, which showed that first-line gefitinib treatment significantly improved the progression-free survival of *EGFR* mutation-positive patients with advanced non-small cell lung cancer compared with treatment with carboplatin and paclitaxel (37). We further showed that the significant difference in progression-free survival of *EGFR* mutation-positive patients according to first-line therapy was not associated with a difference in overall survival likely because all patients treated with systemic chemotherapy as a first-line treatment received gefitinib as a subsequent treatment. This finding suggests that the survival benefit of gefitinib treatment for patients with *EGFR* mutations is substantial, even when the drug is administered as a second-line therapy, and it raises the question of whether gefitinib is more effective in such patients as a first-line therapy or is equally effective when administered after systemic chemotherapy. Cox regression analysis in the present study revealed that progression-free survival after gefitinib treatment was significantly longer in the chemotherapy-naïve patients than in those who had received previous chemotherapy. Although the impact of systemic chemotherapy on the subsequent efficacy of gefitinib in *EGFR* mutation-positive patients remains ill defined, our data raise the possibility that systemic chemotherapy may induce biological effects that lead to gefitinib resistance. Elucidation of such effects will be difficult given the challenges associated with repeated tumor biopsy in non-small cell lung cancer patients after the initiation of chemotherapy. Recent randomized phase III studies found that the tolerability profile of gefitinib was better than that of systemic chemotherapy, resulting in improvement in quality of life (9, 10). Taken together, these data provide support for the treatment of chemotherapy-naïve, *EGFR* mutation-positive non-small cell lung cancer patients with gefitinib, although well-designed randomized trials that compare EGFR tyrosine kinase inhibitors with standard chemotherapy and monitor quality of life in such patients are warranted.

In conclusion, our combined analysis of updated individual patient data from seven Japanese phase II trials confirmed that gefitinib monotherapy yields substantial clinical benefits in terms of a high response rate and prolonged progression-free

survival and overall survival in advanced non-small cell lung cancer patients with *EGFR* mutations. Our results have important potential implications for clinical practice. The median survival time of ~2 years achieved in patients with *EGFR* mutation-positive non-small cell lung cancer by treatment with gefitinib supports the notion that this group of patients constitutes a clinically distinct population. Furthermore, our exploratory comparison between gefitinib and systemic chemotherapy as a first-line treatment suggests that gefitinib monotherapy is a potentially important first-line treatment option for *EGFR* mutation-positive non-small cell lung cancer. We are currently doing phase III randomized studies comparing platinum-based chemotherapy with gefitinib in chemotherapy-naïve non-small cell lung cancer patients with *EGFR* mutations. Such ongoing phase III clinical trials will help determine whether gefitinib monotherapy becomes the standard of care for *EGFR* mutation-positive non-small cell lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Clinical Studies

Irinotecan plus carboplatin for patients with carcinoma of unknown primary site

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Carcinoma of unknown primary site (CUP) is rarely encountered in clinical practice and optimal chemotherapy has not yet been established. This phase II study was conducted to evaluate the efficacy and toxicity of combined irinotecan + carboplatin therapy in chemotherapy-naive patients with CUP. Irinotecan was administered at 60 mg m^{-2} as a 90-min intravenous infusion on days 1, 8 and 15. Carboplatin was administered at an area-under-the curve of 5 mg ml^{-1} min as a 60-min intravenous infusion on day 1. This cycle was repeated every 28 days for up to six cycles. Forty-five patients were enrolled in the study. An intent-to-treat analysis revealed an objective response rate to the treatment of 41.9% (95% confidence interval, 27.0–57.9%). The median time to progression was 4.8 months and the median survival was 12.2 months. The 1- and 2-year survival rates were 44 and 27%, respectively. The most frequent grade 3 or more severe adverse events were leukopaenia (21%), neutropaenia (33%), anaemia (25%) and thrombocytopaenia (20%). Thus, the combination of irinotecan plus carboplatin was found to be active in patients with CUP. Therefore, the regimen may be one of the potentially available chemotherapeutic options for community standard of care in patients with a good performance status.
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Keywords: carboplatin; chemotherapy; irinotecan; unknown primary

Carcinoma of unknown primary site (CUP) represents a group of heterogeneous malignancies that is diagnosed based on the presence of a metastatic disease without an identifiable primary tumour at the time of presentation. Carcinoma of unknown primary site accounts for approximately 3–5% of all newly diagnosed patients with malignancies (Briasoulis *et al*, 2008b).

The prognosis of CUP is generally poor, with a median overall survival time (OS) of approximately 6–12 months. Some of these patients with favourable and unique clinical and/or pathologic features may show prolonged survival with specific treatment approaches (Pavlidis *et al*, 2003). However, most of the patients fit into the category of poor prognosis. Many investigators have made efforts to develop optimal chemotherapeutic regimens based on the empiric approach, and platinum-based combination chemotherapy is considered to be one of the suitable treatment options for a large proportion of these patients (Pavlidis *et al*, 2003).

Irinotecan is a potent inhibitor of DNA topoisomerase I. It exhibits excellent antitumour activity, not only against a broad spectrum of tumours in experimental models (Kano *et al*, 1992; Misawa *et al*, 1995). Carboplatin is an analogue of cisplatin, with less severe non-haematological toxicities (Briasoulis *et al*, 2000; Yonemori *et al*, 2005). No cross-resistance has been found between irinotecan and carboplatin, and a synergistic effect of irinotecan with carboplatin has been shown in *in vitro* studies (Kano *et al*, 1993).

In an earlier study conducted by us, although the combination of docetaxel plus cisplatin produced favourable results in patients with CUP, treatment discontinuation sometimes became necessary because of the renal toxicity induced by cisplatin (Mukai *et al*, 2003; Yakushiji *et al*, 2006). Carboplatin has proven to be as effective as cisplatin against chemosensitive CUP, with an additional advantage of being better tolerated and more convenient in clinical practice (Briasoulis *et al*, 2000). In this study, we report the results of a phase II trial conducted to evaluate the effect of irinotecan plus carboplatin in the treatment for CUP.

PATIENTS AND METHODS

Patients

Patients who had histologically confirmed metastatic carcinoma were eligible for enrollment in this study, if the following evaluations did not reveal a primary site: complete history, physical examination, blood counts and blood chemistry examinations, including serum α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) as tumour markers in both sexes, carbohydrate antigen 125 (CA125) as a tumour marker in women, prostate-specific antigen (PSA) as a tumour marker in men, urinalysis, head and neck examination with pharyngeal

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endoscopy conducted by experienced head and neck surgeons, urologic examination conducted by experienced urologists, mammography in women, gynaecologic examination by experienced gynaecologists in women, chest X-ray, whole-body computed tomography, upper gastrointestinal endoscopy, lower gastrointestinal endoscopy or barium enema, bone scintigraphy and direct workup of any symptomatic area.

Patients were enrolled in the study if they fulfilled the following eligibility criteria: (1) diagnosed as having CUP, (2) chemotherapy naive, (3) age $\geqslant$20 years, (4) life expectancy of at least 3 months, (5) an Eastern Cooperative Oncology Group performance status of $\leqslant$2, (6) the presence of a measurable lesion as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse *et al*, 2000) and (7) adequate organ function (total leukocyte count $\geqslant$3000 per μl or absolute neutrophil count $\geqslant$1500 per μl, platelet count $\geqslant$100 000 per μl, serum total bilirubin $\leqslant$1.5 mg dl^{-1}, serum alanine aminotransferase $\leqslant$2 times the upper limit of normal, serum creatinine $\leqslant$1.5 mg dl^{-1}). Patients with active infection, bowel obstruction, interstitial pneumonitis, uncontrolled severe heart disease, uncontrolled diabetes mellitus, pregnant or lactating women, symptomatic brain metastasis, severe coexistent medical illness or a past history of hypersensitivity to drugs were excluded from the study. Patients who had massive pleural effusion or ascites that required drainage or active concomitant malignancy were also excluded. Patient subgroups that were suitable for well-established treatments (i.e., men with blastic bone metastases showing features of adenocarcinoma and elevated PSA, women with axillary lymph nodes as the only site of disease showing features of adenocarcinoma, woman with papillary serous carcinoma of the peritoneum, patients with either cervical or inguinal lymph node involvement only with features of squamous cell carcinoma, patients with poorly differentiated carcinomas suggestive of germ cell tumour with elevated levels of AFP and/or β-HCG, patients with low-grade, well-differentiated neuroendocrine carcinoma and patients with carcinoma involving a single, potentially resectable site) were also excluded from the study. The protocol was approved by the institutional review board. All patients provided written informed consent before their enrollment.

Treatment

Irinotecan was administered at the dose of 60 mg m^{-2} dissolved in 100 ml saline as a 90-min intravenous infusion, followed by carboplatin at an area-under-the curve of 5 mg ml^{-1} min dissolved in 250 ml of saline or 5% dextrose as a 60-min intravenous infusion. Irinotecan administration was planned for days 1, 8 and 15 of each cycle, and that of carboplatin was planned for day 1 of each cycle. The Calvert formula was used to determine the carboplatin dose, based on the glomerular filtration rate calculated using the serum creatinine level, body weight, age and sex (Cockcroft and Gault, 1976; Calvert *et al*, 1989). Patients showing treatment response or stable disease were administered up to a total of six courses. Granisetron 3 mg and dexamethasone 8 mg were used routinely before the drug infusions as antiemetic agents on days 1, 8 and 15. Prophylactic granulocyte colony-stimulating factor was not used routinely.

Irinotecan and carboplatin were administered on day 1 if the leukocyte count was $\geqslant$3000 per μl or the neutrophil count was $\geqslant$1500 per μl, the platelet count was $\geqslant$75 000 per μl, serum total bilirubin was $\leqslant$1.5 mg dl^{-1}, serum alanine aminotransferase was $\leqslant$2 times the upper limit of normal, the serum creatinine was $\leqslant$1.5 mg dl^{-1} and any non-haematological toxicities, with the exception of alopaecia, were $\leqslant$grade 1. Patients who failed to improve to less than grade 2 in terms of the non-haematological toxicity even after withholding of the treatment for 2 weeks were withdrawn from the study.

Irinotecan was administered on day 8 or 15 if the leukocyte count was $\geqslant$2000 per μl or the neutrophil count was $\geqslant$1000 per μl, the platelet count was $\geqslant$75 000 per μl and any non-haematological toxicities, with the exception of alopaecia, were $\leqslant$grade 1. The dose on day 8 and/or day 15 was omitted entirely if the counts or toxicities did not satisfy the above criteria.

Dose modification of carboplatin from AUC 4 to AUC 5 was allowed if febrile neutropaenia or grade 4 thrombocytopaenia was observed, or if platelet transfusion was required.

Response and toxicity evaluation

All patients were re-evaluated for response after completion of two cycles of treatment, and the response categories were assigned based on the RECIST criteria (Therasse *et al*, 2000). Repeat scans at 8-week intervals were performed to confirm the response. The final response category assigned to these patients represented the best response obtained during the treatment course. Toxicities were evaluated according to the National Cancer Institute's Common Toxicity Criteria, Version 2.0, after every cycle and at the end of the study treatment.

Statistical analysis

The primary end point of this study was the objective response rate, defined as the proportion of patients with complete response or partial response in the intent-to-treat (ITT) population, in turn, defined as patients who had received at least one cycle of irinotecan and carboplatin. The secondary end points included safety and tolerability, time to tumour progression (TTP), OS, and the 1- and 2-year survival rates.

The sample size was determined using Simon's Minimax two-stage design for phase II studies. The response rates to chemotherapy of patients with CUP have been reported as approximately in the range of 20–40% (Briasoulis *et al*, 2000; Greco *et al*, 2000a, b; Dowell *et al*, 2001), so that the null hypothesis was that the true response rate was less than or equal to 30% (not considered to be clinically meaningful). The alternative hypothesis was that the true response rate was more than or equal to 50%. A total of 39 patients were required as the target sample to ensure results with 80% power and a type I error rate of 5%, for rejecting the null hypothesis that the true response probability was less than or equal to 30%. The enrollment of 45 patients was planned to fulfill the requirement of 39 patients, because some patients might need to be potentially excluded from the analysis because of failure to receive at least one cycle of irinotecan and carboplatin.

The objective response rate was reported as a percentage, along with the 95% confidence interval. The TTP and OS were determined by the Kaplan–Meier method. All the statistical analyses were performed using SPSS 12.0J (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Between May 2003 and November 2007, 45 patients were enrolled in this clinical trial. The patient characteristics are listed in Table 1. The median age was 59 years (range, 36–78 years), and the median performance status (PS) was 1 (range, 0–2). The median number of disease sites per patient was two (range, 1–7).

Twenty-three patients had lymph node involvement only. Serum tumour markers were assessed at the baseline pretreatment evaluation in 43 patients. The median number of tumour markers showing elevated serum levels was 5 (range, 0–10). Eighty-seven percent (N=39) of the patients showed elevated serum levels of tumour markers at the time of diagnosis (Table 2).

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Table 1 Patient characteristics

Characteristics	No. of patients
No. of patients enrolled	45
Age (years)	
Median	59
Range	36–78
Sex	
Male	23
Female	22
ECOG performance status	
0	19
1	22
2	4
Histologic type	
Adenocarcinoma (well and moderately differentiated)	21
Poorly differentiated adenocarcinoma	9
Squamous cell carcinoma	7
Poorly differentiated carcinoma	5
Clear cell carcinoma	1
Small cell carcinoma	1
Undifferentiated carcinoma	1
No. of disease sites	
1	13
2	10
⩾3	22
Site of disease	
Lymph node	40
Lung	6
Bone	4
Liver	8
Adrenal	2
Malignant effusion	4
Soft tissue	3
Other	6
Prognostic index	
Culine *et al* (2002a)[a]	
Good risk	29
Poor risk	16
van der Gaast *et al* (1996)[b]	
Good risk	19
Intermediate risk	19
Poor risk	7

ECOG = Eastern Cooperative Oncology Group. [a]Good-risk patients had a performance status of 0 or 1 and normal serum lactate dehydrogenase (LDH) levels; poor-risk patients had a performance status of ⩾2 or elevated serum LDH levels. [b]Good-risk patients had a performance status of 0 and serum alkaline phosphatase (ALP) levels of $<1.25 \times$ normal range (N); intermediate-risk patients had a performance status of ⩾1 or serum ALP levels of $\geqslant 1.25 \times N$; poor-risk patients had a performance status of ⩾1 and serum ALP levels of $\geqslant 1.25 \times N$.

Efficacy

Forty-five patients were enrolled in this study. All the enrolled patients were included in the analysis for TTP and OS, and 43 patients who had received at least one cycle of irinotecan plus carboplatin were assessed for tumour response to treatment. Two patients who were withdrawn from the study because of the appearance of toxicity in cycle 1 were considered as not evaluable. Objective response was observed in 18 patients, including complete response in two and partial response in 16 patients. Stable disease was observed in 10 patients and progressive disease in 15 patients. The results of an ITT analysis revealed an objective response rate of 41.9% (95% confidence interval, 27.0–57.9%); the response rate was 41.3% in the 30 patients with well-to-poorly differentiated adenocarcinoma and 50.0% in the 23 patients with lymph node involvement only. The median TTP was 4.8 months, and the median OS was 12.2 months. The 1- and 2-year survival rates were 44 and 27%, respectively (Figure 1).

Table 2 Elevated serum tumour marker levels at diagnosis

Markers	Normal range	No. of measured patients	No. of patients with elevated levels (%)
AFP	$\leqslant 10\,ng\,ml^{-1}$	42	2 (4.7)
β-HCG	$\leqslant 0.5\,mIU\,ml^{-1}$	42	22 (52.4)
Cyfra	$\leqslant 2.2\,ng\,ml^{-1}$	41	30 (73.2)
SCC	$\leqslant 1.5\,ng\,ml^{-1}$	41	7 (17.1)
NSE	$\leqslant 15\,ng\,ml^{-1}$	42	10 (23.8)
ProGRP	$<46\,pg\,ml^{-1}$	41	8 (19.5)
PSA	$\leqslant 2.7\,ng\,ml^{-1}$	23	5 (21.7)
CEA	$\leqslant 5.0\,ng\,ml^{-1}$	43	19 (44.2)
SLX	$\leqslant 38\,U\,ml^{-1}$	41	21 (51.2)
STN	$\leqslant 45\,U\,ml^{-1}$	41	16 (39)
NCC-ST439	$\leqslant 4.5\,U\,ml^{-1}$	41	16 (39)
CA125	$\leqslant 35\,U\,ml^{-1}$	39	25 (64.1)
CA15-3	$\leqslant 28\,U\,ml^{-1}$	41	12 (29.3)
CA19-9	$\leqslant 37\,U\,ml^{-1}$	43	17 (39.5)
PIVKA-II	$<40\,mIU\,ml^{-1}$	39	2 (5.1)
Elastase	$\leqslant 300\,ng\,dl^{-1}$	41	3 (7.3)

AFP = α-fetoprotein; CA125 = carbohydrate antigen 125; CA15-3 = carbohydrate antigen 15-3; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; Cyfra = cytokeratin 19 fragment; NCC-ST439 = national cancer center-ST439; NSE = neuron-specific antigen; PIVKA-II = protein induced by vitamin K absence-2; ProGRP = progastrin-releasing peptide; PSA = prostate-specific antigen; SCC = squamous-cell carcinoma antigen; SLX = sialyl-specific embryonic antigen; STN = sialyl TN antigen; β-HCG = β-human chorionic gonadotropin.

Toxicity

The toxicity data are listed in Table 3. Bone marrow suppression (leukopaenia, neutropaenia and thrombocytopaenia) and gastrointestinal toxicities, such as nausea, vomiting, diarrhoea and appetite loss, were the most frequent. There were no treatment-related deaths in this study.

Overall, 180 treatment cycles were administered and the median number of cycles per patient was four (range, 1–6). Of the 180 cycles, in 9.4% (17 episodes), the day-8 administration of irinotecan was withheld because of neutropaenia (11.8%), anaemia (5.9%), thrombocytopaenia (35.3%) or non-haematological toxicity (41.1%), including two episodes of fatigue, three episodes of nausea, two episodes of infection and one episode of palpitation. Furthermore, in 27.2% of the cycles, the day-15 administration of irinotecan was withheld because of neutropaenia (14.3%), thrombocytopaenia (65.3%), non-haematological toxicity (16.3%), including one episode of appetite loss, one episode of nausea, two episodes of diarrhoea, four episodes of febrile neutropaenia and patient refusal for personal reasons (two instances). The day-8 or day-15 irinotecan was withheld at least once in 24 (53%) patients. Five patients (11.1%) with anaemia required red blood cell transfusion and four patients (8.9%) with thrombocytopaenia required platelet transfusion. Dose modification of carboplatin was necessary in 15.5% of the patients (seven patients).

DISCUSSION

Recently published trials, in the literature, of regimens containing platinum agents for CUP have reported objective response rates in the range of 13–55% and median OS in the range of 6.0–16.2

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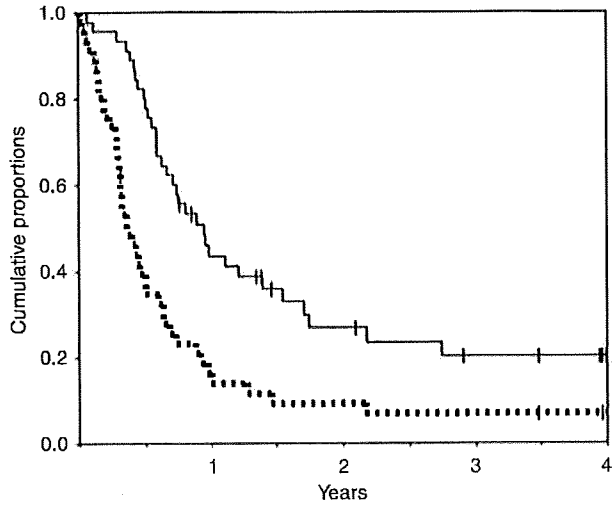

Figure 1 Kaplan–Meier analysis to determine the time to progression (dotted line) and overall survival (solid line).

Table 3 Toxicity profiles (frequency > 10%)

Profile	Frequency (%)	No. of grade 3 (%)	No. of grade 4 (%)
Haematologic toxicity			
Leukopaenia	75.6	6 (13.3)	4 (8)
Neutropaenia	80	6 (13.3)	9 (20)
Anaemia	93.3	8 (17.8)	3 (6.7)
Thrombocytopaenia	68.9	7 (15.6)	2 (4.4)
Non-haematologic toxicity			
Fatigue	60	0 (0)	0 (0)
Appetite loss	46.7	0 (0)	0 (0)
Nausea	82.2	1 (2.2)	0 (0)
Vomiting	26.7	1 (2.2)	0 (0)
Diarrhoea	57.8	4 (8)	0 (0)
Constipation	42.2	0 (0)	0 (0)
Skin rash	20	0 (0)	0 (0)
Febrile neutropaenia	13.3	5 (11.1)	1 (2.2)

months (Table 4). In two of these trials conducted to evaluate the activity of first-line platinum-based combination chemotherapy, the treatment regimen included irinotecan (Culine *et al*, 2003; Briasoulis *et al*, 2008a). According to one, the combination of irinotecan plus cisplatin yielded an objective response rate of 38% and median OS of 6 months (Culine *et al*, 2003). In another study limited to poor-prognosis patients, irinotecan plus oxaliplatin yielded an objective response rate of 13% and median survival time of 9.5 months, with 40% of the patients still alive at 1 year (Briasoulis *et al*, 2008a). The patient background, especially the prognostic characteristics, may have an influence on the treatment outcome. Two-thirds of the patients in this study were prognostically good-risk patients, with a low percentage of patients having liver metastasis and a large percentage of patients with the disease extent being limited to the lymph nodes; in contrast, in most of the recently published series, the majority of the patients were prognostically poor-risk patients and/or had liver metastasis. Therefore, potential bias would make a reliable comparison of the results of the present and previous studies difficult.

Interestingly, the Kaplan–Meier analysis in this study revealed a 2-year survival rate of 27%, with some patients even showing long-term survival (Figure 1). The results of chemotherapy in a total of 1515 patients enrolled in 45 trials including 10 patients or more conducted between 1964 and 2002 showed that survival of the patients beyond 2 years was rare and that there were no cases of disease-free survival beyond 3 years (Pavlidis *et al*, 2003; Greco and Hainsworth, 2008). However, more recent studies have reported long-term survival in a small percentage of patients (Table 4). Long-term follow-up of the 396 patients enrolled in the five most recent studies revealed 1-, 2-, 3-, 5-, 8- and 10-year survival rates of 38, 19, 12, 11, 8 and 8% (Greco and Hainsworth, 2008). Although the reasons for the recent increase in long-term survival are uncertain, it is noteworthy that long-term survival was obtained with the combination of platinum agents and new agents.

The emergence of new non-platinum agents after 1995, including taxanes, gemcitabine, vinorelbine and irinotecan, has enabled the development of platinum-based combination chemotherapy for patients with CUP (Pavlidis *et al*, 2003). However, no definitive conclusions have been reached, because there is still no evidence based on randomised clinical trials to prove the superiority of the aforementioned combination chemotherapies over single-agent platinum therapy. In addition, the clinical benefits and risks of doublet and triplet combination chemotherapies are still uncertain. An attempt was made by European investigators to compare the effect of single-agent cisplatin with that of combined therapy with gemcitabine plus cisplatin on survival in good-risk patients with CUP. Although the results of this prospective trial were expected to clarify the role of combination chemotherapy in good-risk patients with CUP, the trial was stopped due to insufficient accrual, and the result showed a non-significantly higher survival with gemcitabine plus cisplatin as compared to that with cisplatin alone (Gross-Goupil *et al*, 2008).

Recently, standard chemotherapeutic regimens with or without molecular-targeting agents have been established for many cancers. Thus, there is a great demand to optimise the chemotherapeutic regimen for each patient with CUP. The approach based on the genomic characteristics may come to represent one of the breakthroughs in the proper use of chemotherapies tailored to individual patients.

In addition, the advances in the development of many molecular-targeted agents provide opportunities to explore various new combination therapies containing both cytotoxic and molecular-targeted agents for patients with CUP. Several studies have demonstrated the immunohistochemical expression of relevant molecular targets at high frequencies in tissue specimens (Massard *et al*, 2007). A phase II trial of bevacizumab plus erlotinib revealed substantial activity of this combination in patients treated previously or patients who had not received treatment because of the presence of poor-prognostic features (Hainsworth *et al*, 2007). In a preliminary study, treatment with paclitaxel plus carboplatin used in combination with bevacizumab plus erlotinib yielded an objective response rate of 48% ($N = 19$ out of 40) and was well tolerated as first-line chemotherapy for patients with CUP (Greco *et al*, 2008). After first-line platinum-based combination chemotherapy, the approach of empiric second-line chemotherapy has shown little promise, with extremely low response rates (Hainsworth *et al*, 2001, 2005). Therefore, tailor-made first-line chemotherapy by genomic typing or addition of molecular-targeted drugs may be important in the treatment of CUP, which includes heterogeneous cancers, rather than the development of second-line chemotherapy.

In this study, the most frequently encountered toxicity was haematological toxicity and some patients needed blood transfusion or dose reduction of carboplatin. The dose delivery was fairly smooth in the chemotherapy-naive patients with CUP as compared with that in our earlier phase I study of combined irinotecan plus carboplatin in patients with heavily treated ovarian cancer (Yonemori *et al*, 2005). Among the advantages of this regimen are

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Table 4 Clinical trials of first-line regimens containing platinum agents reported in the literature from 2000

Group	Reference	Regimen	N	RR	MST (m)	1 year[a]	2 year[b]
Doublet	Briasoulis *et al* (2000)	Carbo–P	77	38.7%	13.0	NA	NA
	Voog *et al* (2000)	Cis–E	22	32%	8.0	NA	NA
	Greco *et al* (2000a)	Cis–D	26	26%	8.0	40%	28%
		Carbo–D	47	22%	8.0	33%	28%
	Dowell *et al* (2001)	Carbo–E	17	19%	8.3	26%	NA
	Saghatchian *et al* (2001)	Cis–E→Cis–E–B–I	30	40%	9.4	NA	28%
		Cis–F	18	44%	16.1	NA	39%
	Culine *et al* (2002b)	Dx–Cy⇔Cis–E	82	39%	10.0	NA	NA
	Culine *et al* (2003)	Cis–G	39	55%	8.0	NA	NA
		Cis–Ir	40	38%	6.0	NA	NA
	Park *et al* (2004)	Cis–P	37	42%	11.0	38%	11%
	El-Rayes *et al* (2005)	Carbo–P	22	23%	6.5	27%	NA
	Pittman *et al* (2006)	Carbo–G	51	30.5%	7.8	26%	12%
	Briasoulis *et al* (2008a)	Ox–Ir	47	13%	9.5	40%	NA
	Pentheroudakis *et al* (2008)	Carbo–D	47	32%	16.2	NA	NA
	This study	Carbo–Ir	45	41.9%	12.2	44%	27%
Triplet or more	Parnis *et al* (2000)	Cis–F–Ep	43	23%	5.8	NA	NA
	Greco *et al* (2000b)	Carb–P–E	71	48%	11.0	48%	20%
	Guardiola *et al* (2001)	Cis–Dx–Cy	22	50%	10.7	NA	NA
	Macdonald *et al* (2002)	Cis–F–Mit	31	27%	7.7	28%	10%
	Greco *et al* (2002)	Carbo–G–P	113	25%	9.0	42%	23%
	Balaña *et al* (2003)	Cis–G–E	30	36.6%	7.2	26%	NA
	Piga *et al* (2004)	Carbo–Dx–E	102	26.5%	9.0	35.2%	18.1%
	Greco *et al* (2004)	Carbo–P–E→G–Ir	111	33%	9.1	35%	16%
	Palmeri *et al* (2006)	Cis–G–P	33	48.5%	9.6	NA	NA
		Cis–G–V	33	42.3%	13.6	NA	NA
	Schneider *et al* (2007)	Carb–G–Cape	33	39.4%	7.6	35.6%	14.2%
	Greco *et al* (2008)	Carbo–P–Bv–Er	51	48%	11.3	NA	NA

B = bleomycin; Bv = bevacizumab; Cape = capecitabine; Carbo = carboplatin; Cis = cisplatin; Cy = cyclophosphamide; D = docetaxel; Dx = doxorubicin; E = etoposide; Ep = epirubicin; Er = erlotinib; F = 5-FU; G = gemcitabine; I = ifosfamide; Ir = irinotecan; m = months; Mit = mitomycin C; MST = median survival time; NA = not available; Ox = oxaliplatin; P = paclitaxel; RR = response rate; V = vinorelbine. [a]1 year = 1-year survival rate. [b]2 year = 2-year survival rate.

that it is easy to adjust the irinotecan dose during each chemotherapy cycle according to the individual toxicity profiles and to manage the chemotherapy on an outpatient basis without prophylactic use of granulocyte-stimulating factor or erythropoietin.

In conclusion, combined irinotecan plus carboplatin chemotherapy appears to exert satisfactory activity and to be reasonably well tolerated in patients with CUP. Many conventional chemotherapies have been reported as the community standard of care for patients with CUP. This regimen was moderately well tolerated and may become established as one of the treatment options in patients with a good PS.

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Conflict of interest

Katsumata N: Honoraria (Sanofi-aventis, Pfizer, Nippon Kayaku, Kyowa Hakko Kogyo, Zeneca). His family members have no financial interest or conflict of interest in relation to this study. None of the authors or their immediate family members have any financial interest or conflict of interest in relation to this study.

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